

Stimulant Useful for Comorbid ADHD, Bipolar

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New England Bureau

BOSTON — Children and adolescents being treated for bipolar disorder and comorbid attention-deficit/hyperactivity disorder may benefit from the short-term use of adjunctive methylphenidate, a study has shown.

The findings add to the growing body of ev-

idence supporting the concomitant treatment of both conditions. Using methylphenidate to treat patients with bipolar disorder has been the subject of controversy in light of concerns that the use of stimulant drugs in bipolar patients could exacerbate or trigger manic symptoms.

In fact, according to lead author Dr. Robert L. Findling of University Hospitals Case Medical Center, Cleveland, the addition of methylphenidate to monotherapy with either lithium or divalproex sodium (DVPX) or to combination therapy with both drugs "did not cause a destabilization of improved mood symptoms" in the 4-week, double-blind, placebo-controlled trial.

To examine the short-term efficacy of adjunctive methylphenidate in this patient population, Dr. Findling and his colleagues enrolled 20 young people aged 5-17 years who met DSM-IV criteria for bipolar disorder and ADHD. At the time of the investigation, all of the study participants were receiving a stable dose of at least one thymoleptic agent, and continued to have clinically significant symptoms of ADHD while euthymic.

As per study protocol, all of the patients received 1 week each of placebo, 5 mg of methylphenidate twice daily, 10 mg of methylphenidate twice daily, and 15 mg of methylphenidate twice daily using a crossover design, and were randomly assigned to receive one of six possible dos-

The primary outcome measure for the study was the total score on the ADHD Rating Scale-IV (ARS-IV), which was completed by the parents. At the end of the study, before breaking the blind, the investigators determined a "best dose" week for each subject based on this measure.

A total of 16 patients, mean age 10.43 years, completed the trial. Of the 16, 12 were receiving combination therapy with DVPX and lithium, 3 were receiving DVPX monotherapy, and 1 was receiving lithium monotherapy.

To assess efficacy, the investigators compared psychometric ratings for the placebo week with those of the best dose week for each patient and observed significant differences for the ARS-IV Inattentive Subscale, the ARS-IV Impulsivity/Hyperactivity Subscale, and the ARS-IV total scores, indicating a therapeutic benefit, Dr. Findling reported in a poster presentation at the annual meeting of the American Academy of Child and Adolescent Psychiatry.

The investigators also used the Clinical Global Impression (CGI) severity scale to evaluate patient response to the therapy relative to the placebo week. The mean CGI-severity score was significantly lower at the best dose week, compared with the placebo week, "suggesting less psychiatric symptomatology," said Dr. Findling, also of Case Western Reserve University.

The study was supported primarily by the Stanley Medical Research Institute. Study medications were provided, in part, by Abbott Laboratories, Dr. Findling disclosed.

Brief Summary—see package insert for full prescribing information.

ARICEPT* (Donepezil Hydrochloride Tablets)

ARICEPT* ODT (Donepezil Hydrochloride) Orally Disintegrating Tablets

INDICATIONS AND USAGE ARICEPT* is indicated for the treatment of dementia of the Alzheimer's type. Efficacy has been rated in patients with mild to moderate Alzheimer's Disease, as well as in patients with severe Alzheimer's Disease. CONTRAINDICATIONS ARICEPT® is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to idine derivatives. **WARNINGS** *Anesthesia:* **A**RICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type piperione cervatives. WARNINGS Anestnessa: ARILLE-PT, as a cholinesterase inhibitor, silkely to exaggerate succinylcholiners muscle relaxation during anesthesia. Cardiovascular Conditions: Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sincatrial and adrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of ARICEPT". Gastrointestinal Conditions: Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT* nistory of ulcer disease of mose receiving concurrent norisetrolical anti-inframmatory drugs (NSAUS). Unlineal studies of ARICEPT* as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, rausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT*. Genitourinary: Although not observed in clinical trials of ARICEPT*, cholinomimetics may cause bladder outflow obstruction. Neurological Conditions: Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease. Pulmonary Conditions: Secause of their collonomimetic actions, cholinosterese inhibitions should be preceipted with zere to natients with a bistory of asthmac nor obstructive. cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **PRECAUTIONS Drug-Drug Interactions** (see Clinical Pharmacology. Clinical Pharmacokinetics: Drug-drug Interactions) **Effect of ARICEPT* on the Metabolism of Other Drugs**: No in vivo clinical trials have investigated the effect of Interactions) Effect of ARICEPT* on the Metabolism of Uther Drugs: No in vivo clinical trials have investigated the effect of ARICEPT* on the clearance of drugs metabolized by CYP 234 (e.g. cisapride, terfenadine) or by CYP 206 (e.g. imipramine). However, in vitro studies show a low rate of binding to these enzymes (mean K, about 50-130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Whether ARICEPT* has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of ARICEPT* for interaction with theophylline, cimetidine, warfarin, digoxin and keloconazole. No effects of ARICEPT* of the pharmacokinetics of these drugs were observed. Effect of Other Drugs on the Metabolism of ARICEPT* is Ketoconazole and quinidine, inhibitors of CYP450, 344 and 206, respectively interaction in the pharmacokinetic studies are allowed laffect of minidine in other one a 7-deveroper service in 18 belity. inhibit donepezil metabolism in vitro. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy Innibit conepeal measonism in virta winder there is a clinical effect of quinione is not known. In a 7-day crossover study of in 1 research wear of compared there is a clinical effect of the graph of the properties of the proper or cholinergic agonists such as bethanechol. Carcinogenesis, Mutagenesis, Impairment of Fertility No evidence of a or choinergic agonisis such as betrainaerchoil. Carcinogenesis, mutagenesis, imparment or Fernitry No eviolence of carcinogenic potential was obtained in an 88-week carcinogenicity study of done pezial hydrochloride conducted in CD-1 mice at doses up to 180 mg/kg/day (approximately 90 times the maximum recommended human dose on a mg/m² basis), or in a 104-week carcinogenicity study in Spraque-Dawley rats at doses up to 30 mg/kg/day (approximately 90 times the maximum recommended human dose on a mg/m² basis). Donepezil was not mutagenic in the Arnes reverse mutation assay in bacteria, or in a mouse lymphoma forward mutation assay in vitiro. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test and was not genotoxic in an *in vivo* unscheduled DNA synthesis assay in rats. Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the programm generated human dose on a mg/m² bacis. Personance Personance Caronance Caronan maximum recommended human dose on a mg/m^2 basis). **Pregnancy Pregnancy Category C:** Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m^2 basis) and pregnant ratis at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/mr basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/mr basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in astudy in which pregnant ratis were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/mr basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nursing Mothers It is not known whether donepezil is excreted in human breast milk. ARICEPT* has no indication for use in nursing mothers. Pediatrics and a production of the advanced and the prognant women and production of the controlled strains and a significant of the potential benefit justifies the potential risk to the fetus. Nursing Mothers It is not known whether donepezil is excreted in human breast milk. ARICEPT* has no indication for use in nursing mothers. Pediatrics in a significant programment of the prognant prognant in the programment of the prognant prognant prognant programment in the programment prognant prognan Use There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT" in any illness occurring in children.

Geriatric Use Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of the patients enrolled in the clinical studies with ARICEPT" was 73 years; 80% of these patients were between 65 and 84 years old and 49% of the patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups 365 years old and <65 years old. ADVERSE REACTIONS Mild To Moderate Alzheimer's Disease Adverse Events Leading to Discontinuation of the clinical trials of ARICEPT" due to adverse events for the ARICEPT"5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%. The most common adverse events leading to discontinuation defined as those occurring in all tasts 40% cfinated sand tasts to inclinence sans in Javen by adverse events leading to discontinuation of the control of the control of the comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%. The most common adverse events leading to discontinuation of the control of Use There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1, Table 1 Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group (Placebo Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group (Placebo, 5 mg/day ARICEPT", respectively); Patients Randomized (355, 350, 315); Event/% Discontinuing: Nausea (1%, 1%, 3%); Diarrhea (0%, <1%, 3%); Vomiting (<1%, <1%, 2%). Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT". The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT" scholinomimetic effects. These include rausea, diarrhea, insommia, vomiting, muscle cramp, tatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT" treatment without the need for dose modification. The six evidence to suppose that the frequency of these common adverse events may be affected by the rate of titration. An one-public study was to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15 and 30-week studies. These patients were titrated to a dose of 10 mg/day conducted with 269 patients who received placebo in the 15 and 30-week studies. I hese patients were littrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day. See Table 2 for a comparison of the most common adverse events following one and six week titration regimens. Table 2. Comparison of rates of adverse events in patients titrated to 10 mg/day over 1 and 6 weeks (No titration: Placebo [n=315], No titration: 5 mg/day [n=311], One week titration: 10 mg/day [n=315], Six week titration: 10 mg/day [n=269], respectively): Nausae (6%, 5%, 19%, 6%); Diarrhea (5%, 8%, 15%, 9%); Insomnia (6%, 6%, 14%, 6%); Fatigue (3%, 4%, 8%, 3%); Vorniting (3%, 3%, 8%, 5%); Muscle cramps (2%, 6%, 8%, 3%); Anorexia (2%, 3%, 7%, 3%). Adverse Events Reported in Controlled Trials The events that distributed in the patients of the patients of the distributed in the patients of the patients of the distributed in the patients of the Musclecramps (2%, 6%, 8%, 3%); Anorexia (2%, 3%, 7%, 3%). Adverse Events Reported in Controlled Trials The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In activation of patients treated may differ. Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT* and for which the rate of occurrence was greater for ARICEPT* assigned than placebo assigned patients. In general, adverse events occurred more frequently in fernale patients and with advancing age. Table 3. Adverse Events Reported in Controlled Clinical Trials in Milid to Moderate Alzheimer's Disease in at Least 2% of Patients Receiving ARICEPT* and at a Higher Frequency than Placebo-treated Patients (Body System/Adverse Event: Placebo [n=355], ARICEPT* [n=747], respectively): Percent of Patients with any Adverse Event: 72, 74. Body as a Whole: Headache (9, 10); Pain, various locations (8, 9); Accident (6, 7); Falique (3, 5). Cardiovascular System: Systems: Operations and the second process of the patient of the patients of the patient as a wnote: Headacre (9, 10); Pain, Varous locations (8, 9); Accident (6, 7); Failgue (3, 5); Cartiovascular System: Syntope (1, 2). Digestive System: Nausea (6, 11); Diarrhea (5, 10); Vomiting (3, 5); Anorexia (2, 4). Hemic and Lymphatic System: Ecchymosis (3, 4). Metabolic and Nutritional Systems: Weight Decrease (1, 3). Musculoskeletal System: Muscle Cramps (2, 6); Arthritis (1, 2). Nervous System: Insomnia (6, 9); Dizziness (6, 8); Depression (<1, 3); Abnormal Dreams (0, 3); Somnolence (<1, 2). Urogenital System: Frequent Urination (1, 2). Other Adverse Events Observed During Clinical Trials. ARICEPT* has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials

in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days. Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and two open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These of standardized categories using a modified UCSTART incitionary and event frequencies were calculated across an studies. The categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT*. All adverse events occurring at teast twice are included, except for those afready listed in Tables 2 or 3, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and tisted using the following definitions: frequent adverse events—those occurring in at least 1/100 patients; infrequent adverse events are not necessarily related to ARICEPT* treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States. **Body as a Whole:** Frequent: influenza, chest pain, toothache; Infrequent: Future, advant adverse, predictivity adverse, and a proposition of the pro fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness Cardiovascular System: Frequent: hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension: Infrequent: angina Carolovascular System: Frequent: hyperension, vasocilation, atmin incritation, not lasense, hypotension; imrequent: angine pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, ateritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis. Digestive System: Frequent: feed incontinence, gastrointestinal bleeding, bloating, epigastric pain; Infrequent: eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, lieus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer. Endocrine System: Infrequent: diabetes mellitus, goiter. Hemic and Lymphatic System: Infrequent: anemia, thrombocythemia thrombocytopenia, eosinophilia, erythrocytopenia. Metabolic and Nutritional Disorders: Frequent: dehydration; Infrequent gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. Musculoskeletal System: Frequent: bone fracture; Infrequent: muscle weakness, muscle fasciculation. Nervous System: Frequent: delusions, System: Frequent: bone tracture; Interquent: muscle weakness, muscle tasciculation. Nervous System: Frequent: delusions, tremor, irritability, paresthesia, aggression, vertigo, alaxia, increased libido, restlessness, abnormal crying, nervousnesa, aphasia; Infrequent: cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neurolagia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. Respiratory System: Frequent: dyspnea, sorethroat, bronchitis; Infrequent: epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, sonoring. Stin and Appendages: Frequent: prurius, disphanesis unicipative interval in una deligation should be proposed to the proposed proposed to the proposed proposed in una deligation should be proposed to the proposed diaphoresis, urticaria; Infrequent: dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses:** Frequent: cataract, eye irritation, vision blurred; Infrequent: dry hirsutism, skin striae, ingirt sweats, skin uicer. Special Senses: *requent: cataract, eye irritation, vision blurred; *Imrequent: or yess, glaucoma, earache, tinnitus, bjepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. *Urogenital System: *Frequent: urinary incontinence, nocturia; *Infrequent: dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal tailure, vaginitis. *Severe Alzheimer's Disease Adverse Events Leading to Discontinuation: The rates of discontinuation from controlled clinical trials of ARICEPT" due to adverse events for the ARICEPT" patients were approximately 12% compared to 7% for placebo patients. The most common adverse events leading to discontinuation, defined as those occurring in at least 29% of ARICEPT" patients and at twice the incidence seen in each post discontinuation. *Line of the continuation of the c placebo patients, were anorexia (2% vs 1% placebo), nausea (2% vs <1% placebo), diarrhea (2% vs 0% placebo), and urinary tract placebop patients, were anorexia (2% vs 1% placebo), and unrary fract infection (2% vs 1% placebo). Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT* The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving ARICEPT* and twice the placebo rate, are largely predicted by ARICEPT* scholinomimetic effects. These include diarrhea, anorexia, vorniting, rausea, and ecchymosis. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT* treatment without the need for dose modification. Adverse Events Reported in Controlled Trials Table 4 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT* and for which the rate of eccurronce was creater for ARICEPT* as cincend than placebo-controlled trials. Table 4. Adverse Events Reported in occurrence was greater for ARICEPT* assigned than placebo assigned patients. Table 4. Adverse Events Reported in Controlled Clinical Trials in Severe Alzheimer's Disease in at Least 2% of Patients Receiving ARICEPT* and at a Controlled Clinical Trails in Severe Alzheimer's Disease in at Least 2% of Patients Receiving ARICEPT" and at a Higher Frequency than Placebo-freated Patients (Body System/Adverse Event: Placebo [n=392], ARICEPT" [n=501], respectively): Percent of Patients with any Adverse Event: 73, 81. Body as a Whole: Accident (12, 13); Infection (9, 11); Headache (3, 4); Pain (2, 3); Back Pain (2, 3); Fever (1, 2); Chest Pain (<1, 2). Cardiovascular System: Hypertension (2, 3); Hemorrhage (1, 2); Syncope (1, 2). Digestive System: Diarrhea (4, 10); Vomiting (4, 8); Anorexia (4, 8); Nausea (2, 6), Hemic and Lymphatic System: Ecchymosis (2, 5). Metabolic and Nutritional Systems: Creatine Phosphokinase Increased (1, 3); Dehydration (1, 2); Hyperipemia (<1, 2). Nervous System: Insomnia (4, 5); Hostility (2, 3); Menopuspases (2, 3); Hallucinations (1, 3); Somonlenge (1, 2); Dizigness (1, 2); Dengession (1, 2); Confusion (1, 2); Emortional Lability. Nervousness (2, 3); Hallucinations (1, 3); Somnolence (1, 2); Dizziness (1, 2); Depression (1, 2); Confusion (1, 2); Emotional Lability (1, 2); Personality Disorder (1, 2). Skin and Appendages: Eczema (2, 3). Urogenital System: Urinary Incontinence (1, 2). Other Adverse Events Observed During Clinical Trials ARICEPT® has been administered to over 600 patients with severe Alzheimer's Adverse Events unserved burning climical mars Antice? This deet administration over our platents with severe Authenties? Disease during clinical trials of at least 6 months duration, including 3 double blind placebo controlled trials, one of which had an open label extension. All adverse events occurring at least twice are included, except for those already listed in Table 4, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system using the COSTART dictionary and listed using the following definitions: frequent adverse events—those occurring in at least 1/100 patients; infrequent adverse events—those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEP? "treatment of the patients the patients of the patients of the patients." in most cases were observed at a similar frequency in placebo-freated patients in the controlled studies. **Body as a Whole:** Frequent abdominal pain, asthenia, fungal infection, flu syndrome; Infrequent-allergic reaction, cellulitis, malaise, sepsis, face edema, hernia. **Cardiovascular System:** Frequent: hypotension, bradycardia, ECG abnormal, heart failure; Infrequent: myocardial infarction, Cardiovascular System: Prequent: hypotension, oraqvarida, e.c. a abinoma, heat railure; minequent: hypotendra infancia, angina pectoris, atrial fibrillation, congestive heart failure, peripheral vascular disorder; supraventricular extrasystoles, ventricular extrasystoles, cardiomegaly. Digestive System: Frequent constigation, gastroenteritis, fecal incontinence, dyspepsia; Infrequent, gamma glutamyl transpeptidase increase, gastritis, dysphagia, periodontitis, stomach ulcer, periodontal abscess, flatulence, liver function tests abnormal, eructation, esophagitis, rectal hemorrhage. Endocrine System: Infrequent: diabetes mellitus. Hemic and Lymphatic System: Frequent: anemia, Infrequent: leukoytosis. Metabolic and Nutritional Disorders: Frequent: weight loss, a considerate despendence and despendence of the second despendence of the despendence of the second despend peripheral edema, edema, lactic dehydrogenase increased, alkaline phosphatase increased; *Infrequent:* hypercholesteremia, hypokalemia, hypoglycemia, weight gain, bilirubinemia, BUN increased, B₁₂ deficiency anemia, cachexia, creatinine increased, gout, hyponatremia, hypoproteinemia, iron deficiency anemia, SGOT increased, SGPT increased, Musculoskeletal System: Frequent hypoprotermia, hypoproteinemia, iron deniciency anemia, \$GU increased, \$GP1 increased. Musculoskefetal System: Frequent arthritis; Infrequent: arthrosis, bone fracture, arthraligia, leg cramps, osteoporosis, myalgia. Nervous System: Frequent agalation, anxiety, tremor, corvulsion, wandering, abnormal gait, Infrequent: apathy, vertigo, delusions, abnormal dreams, cerebrovascular accident, increased salivation, atxiae, euphoria, vasodilatation, cerebral hemorrhage, cerebral infarction, cerebral ischemia, dementia, extrapyramidal syndrome, grand mal comvulsion, hemiplegia, hypertonia, hypokinesia. Respiratory System: Frequent: Prayanytiis, preumonia, ought increased, bronchitis; Infrequent: dyspnea, rithitis, asthma. Skin and Appendages: Frequent: rash, skin ulcer, pruritus; Infrequent: onjunctivitis, glaucoma, abnormal vision, ear pain, lacrimation disorder. Urogenital System: Frequent urinary infection custifis hematuria ulcerular valoritis; devirus uricans frequency, altuminuria Pastintraquettion Parants. infection, cystitis, hematuria, glycosuria; Infrequent: vaginitis, dysuria, urinary frequency, albuminuria. Postintroduction Reports
Voluntary reports of adverse events temporally associated with ARICEPT*that have been received since market introduction that are
not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal
pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pain, agination, crolecystuss, confusion, convusions, rationations, read tooks (all types), ferthogocalemia, repailus, ripportations, neuroleptic malignant syndrome, pancreatitis, and rash. OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinestic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may wearness is a possioniny and may result in death if respiratory muscles are involved. Territary articioninergics such as atropine may be used as an antidote for ARICEPT" overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Alypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT" and/or its metabolities can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofilitration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering galt, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature.